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(71) Applicant: FUJI PHOTO FILM CO., LTD.
No. 210, Nakanuma
Minami-Ashigara-shi
Kanagawa-ken (JP)

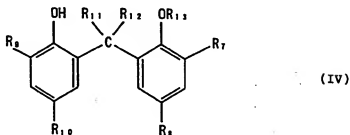
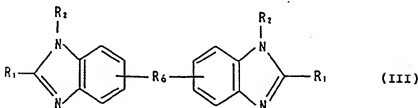
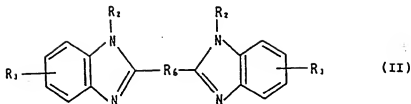
(72) Inventor: Aikawa, Kazuhiro, c/o Fuji Photo
Film Co., Ltd.
No. 210, Nakanuma
Minami-Ashigara-shi, Kanagawa-ken (JP)
Inventor: Aoki, Kozo, c/o Fuji Photo Film Co.,
Ltd.
No. 210, Nakanuma
Minami-Ashigara-shi, Kanagawa-ken (JP)

(73) Representative: Hansen, Bernd, Dr.
Dipl.-Chem. et al
Hoffmann, Eitle & Partner,
Patentanwälte,
Arabellastrasse 4
D-81925 München (DE)

(54) Pharmaceutical composition and method for treating hyperlipidemia and arteriosclerosis.

(57) Disclosed are an antihyperlipidemia or antiarteriosclerosis agent comprising a certain benzimidazole or 2,2'-methylenebisphenol derivative such as 5-dodecanoylamino-2-mercaptobenzimidazole or 2,2'-isobutylidenebis-(4,6-dimethylphenol).

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wherein

35 R_1 represents a hydrogen atom, an alkyl, an aryl, a mercapto, an alkythio, an alkenylthio, an arylthio or a heterocyclo group;

R_2 represents a hydrogen atom or an alkyl group, provided that the alkyl group is not substituted by a hydroxyl group;

40 R_3 and R_4 each independently represents a hydrogen atom, a halogen atom, a nitro group, R_5O- , R_5CONH- , R_5NHCO- , $(R_5)_2NCO-$, R_5SO_2NH- , R_5NHSO_2- , R_5OCO- , R_5COO- or $R_5NHCONH-$ where R_5 represents an alkyl or an aryl group;

R_6 represents a divalent group;

45 R_7 , R_8 , R_9 and R_{10} each independently represents an alkyl, a cycloalkyl group, $-(CH_2)_k-(CH_2)_mCOOR_{14}$ or $-(CH_2)_k-(CH_2)_mCON(R_{14})_2$ where k represents 0 or 1, m represents an integer of 0 to 4 and R_{14} represents a lower alkyl group;

R_{11} and R_{12} each independently represents a hydrogen atom, an alkyl, an aryl or an aralkyl group; and

R_{13} represents a hydrogen atom, a lower alkyl, an aralkyl, an acyl, an alkyl- or arylsulfonyl group, or $-(CH_2)_nCOOR_{15}$ where n represents an integer of 0 to 2 and R_{15} represents a lower alkyl group.

50 The second aspect of the present invention relates to a use of a compound of the formula (I), (II) or (III), or a pharmaceutically-acceptable salt thereof, or a compound of the formula (IV) for preparing an antihyperlipidemia or antiarteriosclerosis agent.

Detailed explanation of preferred Embodiments

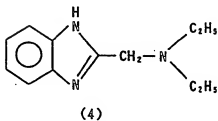
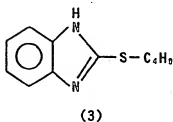
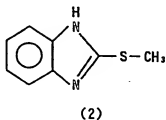
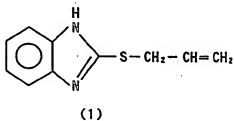
55 The present invention provides a pharmaceutical composition which has an excellent blood cholesterol lowering effect and macrophage-foaming reaction suppressing effect and is low in toxicity, it therefore exhibits an excellent therapeutic effect on hyperlipidemia and arteriosclerosis and is administrable over a long period.

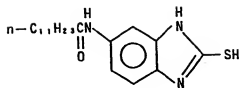
$-(CH_2)_n-$ and $-NHCO(CH_2)_n CONH-$ where n is 2 to 8 are particularly preferable.

Among the above-described compounds having R_1 to R_6 , preferred are the compounds in which at least one substituent has not less than 4 carbon atoms, particularly those in which at least one substituent except for R_2 has 4 to 20 carbon atoms, preferably 8 to 18 carbon atoms.

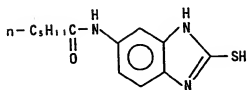
Examples of the pharmaceutically-acceptable salts of the compounds represented by the formulae (I), (II) and (III) include hydrochloride, hydrobromide, nitrate, sulfate and toluenesulfonate. Hydrochloride is particularly preferable.

Examples of the compounds of the formulae (I), (II) and (III) or the formula (V) of the present invention are listed below.

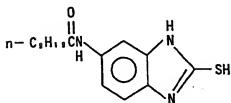




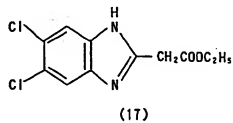
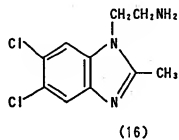
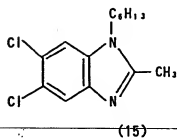
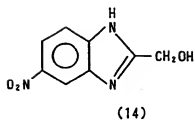
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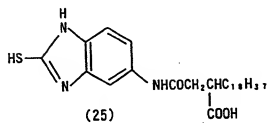
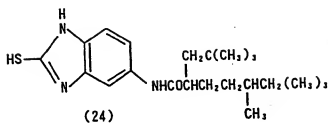
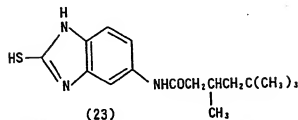
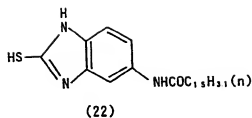


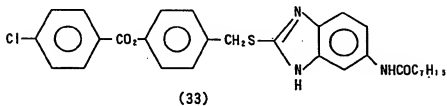
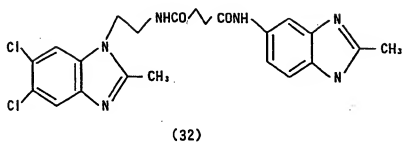
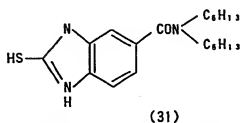
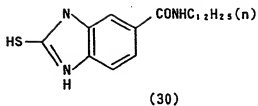
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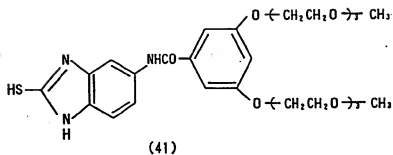
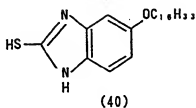
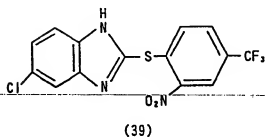
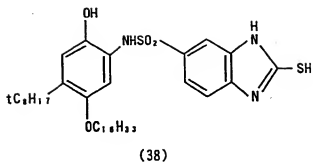


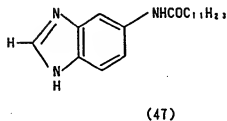
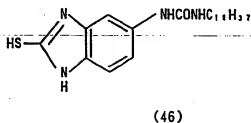
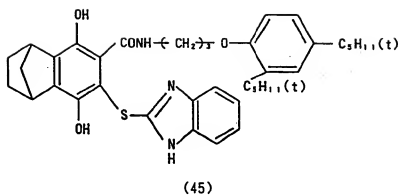
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like). These alkyl groups may be optionally substituted. Examples of the substituents include halogen atoms such as chlorine, bromine, fluorine and iodine.

The cycloalkyl groups represented by R_7 to R_{10} include cyclopentyl, cyclohexyl and cycloheptyl groups. These cycloalkyl groups may be optionally substituted. Examples of the substituents include lower alkyl groups such as methyl and ethyl groups and halogen atoms such as chlorine, bromine, fluorine and iodine. Cycloalkyl groups substituted by methyl group are preferred.

When R_7 to R_{10} represent $-(C(CH_3)_2)_k-(CH_2)_m-COOR_{14}$ or $-(C(CH_3)_2)_k-(CH_2)_m-CON(R_{14})_2$, the lower alkyl groups represented by R_{14} include alkyl groups having 1 to 4 carbon atoms which may be straight or branched chains. Examples of the alkyl groups include methyl, ethyl, n-propyl, isopropyl, isobutyl, sec-butyl and tert-butyl groups, preferably methyl and ethyl groups. k is preferably 1 and m is preferably 3.

Preferable groups represented by R_7 to R_{10} are alkyl groups having 1 to 4 carbon atoms and cycloalkyl groups substituted by methyl group, particularly methyl and tert-butyl groups.

The alkyl groups represented by R_{11} and R_{12} in the formula (IV) include alkyl groups having 1 to 13 carbon atoms which may be straight or branched chains. Examples of the alkyl groups include methyl, ethyl, n-propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, hexyl, octyl, decyl and dodecyl groups. Among these, alkyl groups having 1 to 8 carbon atoms are preferred and those having 1 to 4 carbon atoms are particularly preferred.

The aryl groups represented by R_{11} and R_{12} include phenyl, tolyl, xylyl and naphthyl groups. Phenyl group is preferable.

The aralkyl groups represented by R_{11} and R_{12} include benzyl and phenethyl groups.

In the preferable combination of R_{11} and R_{12} , one is a hydrogen atom and the other is a lower alkyl group having 1 to 4 carbon atoms.

The lower alkyl groups represented by R_{13} in the formula (IV) include alkyl groups having 1 to 4 carbon atoms which may be straight or branched chains. Examples of the alkyl groups include methyl, ethyl, n-propyl, isopropyl, isobutyl, sec-butyl and tert-butyl groups. Methyl and ethyl groups are preferable.

The aralkyl groups represented by R_{13} include benzyl and phenethyl groups.

The acyl groups represented by R_{13} include aliphatic and aromatic acyl groups. Examples of the aliphatic acyl groups include acyl groups having 2 to 6 carbon atoms (such as acetyl, propionyl, pentanoyl and the like), which may be straight or branched chains. Examples of the aromatic acyl groups include benzoyl group. These acyl groups may be optionally substituted. Examples of the substituents of the aliphatic acyl groups include lower alkoxy groups and phenoxy group. These substituents may further be substituted by one or more substituents including lower alkyl groups such as methyl, ethyl, n-propyl, isopropyl, isobutyl, sec-butyl and tert-butyl groups and halogen atoms such as chlorine, bromine, fluorine and iodine. Examples of the substituents of the aromatic acyl groups include lower alkyl groups such as methyl, ethyl, n-propyl, isopropyl, isobutyl, sec-butyl and tert-butyl groups and halogen atoms such as chlorine, bromine, fluorine and iodine.

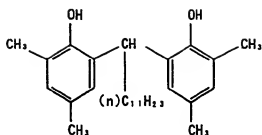
Examples of the alkylsulfonyl groups represented by R_{13} include alkylsulfonyl groups having 2 to 4 carbon atoms (such as methanesulfonyl, ethanesulfonyl, propanesulfonyl and the like), which may be straight or branched chains. Examples of the arylsulfonyl groups represented by R_{13} include benzenesulfonyl and p-toluenesulfonyl groups.

When R_{13} represents $-(CH_2)_n-COOR_{15}$, the lower alkyl groups represented by R_{15} include alkyl groups having 1 to 4 carbon atoms which may be straight or branched chains. Examples of the alkyl groups include methyl, ethyl, n-propyl, isopropyl, isobutyl, sec-butyl and tert-butyl groups. Methyl and ethyl groups are preferable. n is preferably 0 or 1.

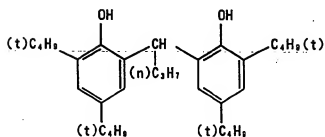
R_{13} is preferably a hydrogen atom.

Examples of the compounds of the general formula (IV) of the present invention are listed below.

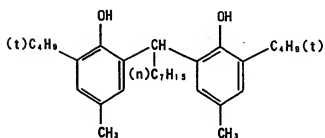
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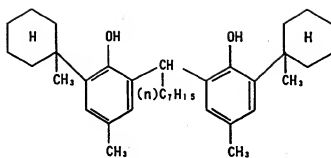
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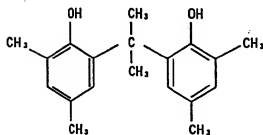
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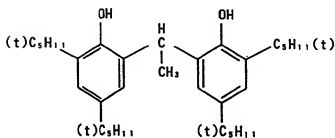
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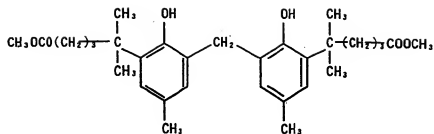
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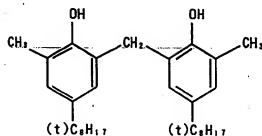
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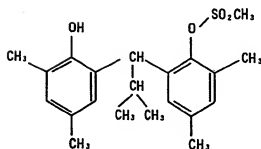
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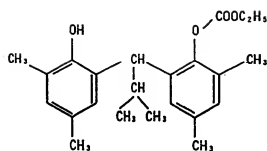
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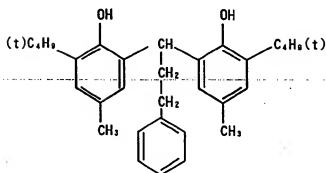
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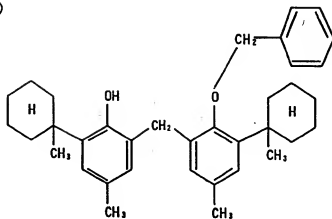
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(74)



(75)



Elemental analysis (%):	Anal.	C 60.62	H 19.25	N 5.41
	Cal.	C 60.54	H 19.26	N 5.54

Synthesis Example 3 Synthesis of 2-mercapto-5-methoxybenzimidazole(13)

70 ml of ethanol and 15 ml of carbon disulfide were added to 2.6 g of 3,4-diaminanisole and then a solution of 1.5 g of sodium hydroxide in 5 ml of water was added thereto. After heating with a water bath for 3.5 hours, the mixture was cooled with ice, filtered and then the solvent in the filtrate was distilled off under reduced pressure. The residue was dissolved in ethanol. The solution was filtrated to remove the insoluble matter and then the solvent in the filtrate was distilled off under reduced pressure. The residue was recrystallized from water-containing methanol to obtain 2.0 g of the titled compound (13).
Melting point : 254-255 °C

Elemental analysis (%):	Anal.	C 53.06	H 4.52	N 15.27
	Cal.	C 53.33	H 4.44	N 15.56

Synthesis Example 4 Synthesis of 2-benzylthiobenzimidazole (7)

15 g of 2-mercaptobenzimidazole and 16.5 g of benzylbromide were dissolved in 50 ml of ethanol and the mixture was refluxed with a water bath for 5 hours. After cooling, the formed crystals were collected and recrystallized from ethanol to obtain 18 g of compound (7).
Melting point : 185-186 °C

Elemental analysis (%):	Anal.	C 69.59	H 5.30	N 11.74
	Cal.	C 69.99	H 5.03	N 11.66

Synthesis Example 5 Synthesis of 5-dodecanoylamino-2-mercaptobenzimidazole (8)

5 g of 5-amino-2-mercaptobenzimidazole was dissolved in 50 ml of pyridine and 7.95 g of dodecanoyl chloride was added dropwise thereto under cooling with ice. After stirring for 3 hours at room temperature, the solution was poured into ice-water. The formed crystals were filtered off and recrystallized from water-containing methanol to obtain 10.9 g of compound (8).
Melting point : 266-267 °C

Elemental analysis (%):	Anal.	C 66.38	H 8.54	N 11.34
	Cal.	C 65.71	H 8.36	N 12.10

Synthesis Example 6 Synthesis of 2-morpholinomethylbenzimidazole (36)

To 108 g of o-phenylenediamine, 1 l of 4 N hydrochloric acid and 142 g of chloroacetic acid were added and refluxed for 1.5 hours. After allowing to stand overnight, the solution was diluted with 2 l of water and neutralized with dilute ammonia water. The formed crystals were filtered off to obtain 113 g of 2-chloromethylbenzimidazole.

10 g of 2-chloromethylbenzimidazole thus obtained and 10.5 g of morpholine were dissolved in 75 ml of alcohol and the solution was refluxed for 3 hours. After cooling, ether was added to the solution and the precipitated crystals were filtered off. The filtrate was washed with water and satulated with hydrogen chloride to form an oily matter. The oily matter was crystalized by adding a small amount of alcohol and the crystals were filtered off. The crystals were recrystallized from alcohol to obtain 2.5 g of compound (36).
Melting point : 235-236 °C

	Compound No.	m.p.(°C)	Compound No.	m.p.(°C)
5				
	(1)	195-200 (HCl salt)	(2)	200-203
10	(3)	133-135 (HBr salt)	(4)	167-170
	(5)	220-221	(6)	135-137
	(7)	190-191	(8)	226-267
15	(9)	266-268	(10)	275-276
	(11)	>300	(12)	>280
	(13)	254-255	(14)	128-129
20	(15)	95-97	(16)	106-108
	(17)	181-183	(18)	119-123
25	(20)	84-87	(21)	183-186
	(23)	250-252	(24)	214-217
	(25)	200 (decomp.)	(26)	284-286
30	(27)	230-232	(28)	132-134
	(29)	217 (decomp.)	(30)	243-245
	(31)	143-144	(32)	>250
35	(33)	124-125	(34)	218-220
	(35)	215-217 (HCl salt)	(36)	235 (decomp.)
40				(HCl salt)
	(37)	162-164	(38)	215-216
	(39)	202-203	(42)	230-231
45	(43)	155-156	(44)	163-164
	(45)	146 (decomp.)	(46)	197-199
	(47)	54-56	(48)	60-63
50	(49)	82-85	(50)	188-191

55

Pharmaceutical test

(1) *In vitro* test for suppressing effect of macrophage-foaming reaction using mouse abdominal cavity macrophage

A 15-week old ICR female mouse (Japan SLC) was amputated at its neck and exsanguinated. Then, Hanks buffer (Nissui Pharmaceutical Co., Ltd.) was injected intraperitoneally. After massaging the abdominal part, the buffer was recovered rapidly and centrifuged at 1,000 rpm for 5 minutes to collect the abdominal cavity macrophage. Then, the collected abdominal cavity macrophage was suspended in GIT medium (Wako Pure Chemical Industry) and inoculated on a 24-well microplate. After culturing the macrophage for 2 hours at 37 °C in 5 % CO₂, the medium was changed into Dulbecco modified Eagle's MEM medium (Nissui Pharmaceutical Co., Ltd.). After further culturing the macrophage for 16 hours at 37 °C in 5 % CO₂, the following substances were added in order:

① Test compounds: solutions in DMSO (Wako Pure Chemical Industry)

1 ml of the solutions were prepared, optionally diluted and the diluted solutions were added to individual wells (500 μ l) in the amount of 5 μ l.

② Liposome

PC/PS/DCP/CHOL. = 50/50/10/75 (nmol)

PC : phosphatidylcholine (Funakoshi)

PS : phosphatidylserine (Funakoshi)

DCP : dicyetylphosphate (Funakoshi)

CHOL : cholesterol (Sigma)

③ ³H-Oleic acid (Amersham Japan)

Then, after still further culturing the macrophage for 16 hours at 37 °C in 5 % CO₂, the lipid fraction was extracted with chloroform and methanol. The extracted lipid fraction was subjected to TLC (hexane:ether:acetic acid = 70:30:1), the separated bands of CE (cholesteryl ester) and TG (triglyceride) were borne off from the TLC plate and then the radioactivities thereof were measured using a liquid scintillation counter (PACKARD BH-22). Yields of cholesteryl ester were calculated by comparing with a control. The results are shown in Table 1.

	(61)	5 μ M	52	103
	(62)	5 μ M	61	98
5	(63)	5 μ M	42	96
	(65)	5 μ M	38	101
10	(66)	5 μ M	54	108
	(67)	5 μ M	42	92
	(68)	5 μ M	53	86
15	(73)	5 μ M	48	90
	(74)	5 μ M	65	108

It is clear from Table 1 that these compounds do not lower the yield of TG so far, that is, these compounds are low toxic and capable of markedly suppressing the yield of CE. Namely, these compounds markedly suppress the macrophage-foaming reaction without being highly toxic to the macrophage.

(2) Blood lipid lowering effect in rabbit fed high-cholesterol feed

(i) New Zealand White female rabbits having body weight of about 2 kg were fed feed having high cholesterol content (100g/day/rabbit: ORC-4 manufactured by Oriental Yeast, containing 0.5 % of cholesterol and 0.5 % of olive oil) for 7 days to produce hypercholesterolemia.

Subsequently, one group consisting of 3 rabbits (treatment group) was fed the same feed in the same amount, except that the feed further contained test compound (8) in the amount of 10 0mg/kg/day/rabbit, for 7 successive days. On the other hand, as a control, another group consisting of 3 rabbits was fed the same feed in the same amount without any test compound.

A small amount of blood was drawn from the parotic vein of every rabbit once a week and was measured for amount of blood total cholesterol using IATROLIPO TC manufactured by latron Laboratories Inc.

The amount of blood total cholesterol of the treatment group fell by 25 % in comparison with the control group (3 rabbits).

Thus, it is clear that test compound (8) has an excellent lowering effect of the blood cholesterol.

(ii) New Zealand White female rabbits having body weight of about 2 kg were fed feed having high cholesterol content (100g/day/rabbit: ORC-4 manufactured by Oriental Yeast, containing 0.5 % of cholesterol and 0.5 % of olive oil) for 7 days to produce hypercholesterolemia.

Subsequently, one group consisting of 3 rabbits (treatment group) was fed the same feed in the same amount, except that the feed further contained test compound (53) in the amount of 1 00mg/kg/day/rabbit, for 7 successive days. On the other hand, as a control, another group consisting of 3 rabbits was fed the same feed in the same amount without any test compound.

A small amount of blood was drawn from the parotic vein of every rabbit once a week and was measured for amount of blood total cholesterol using IATROLIPO TC manufactured by latron Laboratories Inc.

The amount of blood total cholesterol of the treatment group fell by 40 % in comparison with the control group (3 rabbits).

In the same manner, Probucol, a conventional drug, was successivly administered in the amount of 100mg/kg/day for 7 days. In this case, the amount of blood total cholesterol of the treatment group fell by 15 to 20 % in comparison with the control group.

Thus, it is clear that test compound (53) has an excellent blood cholesterol lowering effect in comparison with the conventional drug.

Examples

Example 1 Tablet

5 Preparation of tablet containing 25 mg of compound (8)

① compound (8)	10 g
② corn starch	40 g
③ crystalline cellulose	45 g
④ calcium carboxymethyl cellulose	4 g
⑤ light silicic acid anhydride	500 mg
⑥ magnesium stearate	500 mg
	Total 100 g

① to ⑥ were homogeneously mixed and the resulting mixture was compression molded with a tableting machine to obtain tablets having weight of 250 mg. Each of these tablets contained 25 mg of compound (8). An adult may take 5 to 30 tablets over the course of one day.

20 Example 2 Tablet

Preparation of tablet containing 25 mg of compound (53)

① compound (53)	10 g
② corn starch	40 g
③ crystalline cellulose	45 g
④ calcium carboxymethyl cellulose	4 g
⑤ light silicic acid anhydride	500 mg
⑥ magnesium stearate	500 mg
	Total 100 g

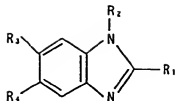
① to ⑥ were homogeneously mixed and the resulting mixture was compression molded with a tableting machine to obtain tablets having weight of 250 mg. Each of these tablets contained 25 mg of compound (53). An adult may take 5 to 30 tablets over the course of one day.

Example 3 Capsule

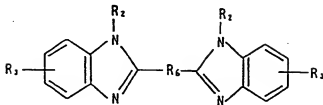
40 Preparation of capsule containing 40 mg of compound (8)

① compound (8)	20 g
③ corn starch	79.5 g
③ light silicic acid anhydride	500 mg
	Total 100 g

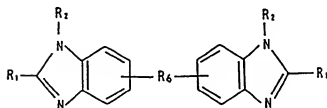
① to ③ were homogeneously mixed and the resulting mixture was encapsulated in the amount of 200 mg per capsule. Each of thus-obtained capsules contained 40 mg of compound (8). An adult may take 1 to 20 capsules over the course of one day.



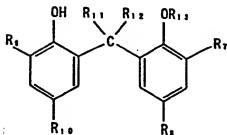
(I)



(II)



(III)



(IV)

wherein

R_1 represents a hydrogen atom, an alkyl, an aryl, a mercapto, an alkythio, an alkenylthio, an arylthio or a heterocyclo group;

R_2 represents a hydrogen atom or an alkyl group, provided that the alkyl group is not substituted by a hydroxyl group;

R_3 and R_4 each independently represents a hydrogen atom, a halogen atom, a nitro group, R_5O- , R_5CONH- , R_5NHCO- , $(R_5)_2NCO-$, R_5SO_2NH- , R_5NHSO_2- , R_5OCO- , R_5COO- or $R_5NHCONH-$ where R_5 represents an alkyl or an aryl group;

R_6 represents a divalent group;

R_7 , R_8 , R_9 and R_{10} each independently represents an alkyl, a cycloalkyl group, $-(C(CH_3)_2)_k-(CH_2)-$, $-mCOOR_{14}$ or $-(C(CH_3)_2)_k-(CH_2)_mCON(R_{14})_2$ where k represents 0 or 1, m represents an integer of 0 to 4 and R_{14} represents a lower alkyl group;

R_{11} and R_{12} each independently represents a hydrogen atom, and alkyl, an aryl or an aralkyl group; and

10. A use of compound of the formula (I), (II) or (III), or a pharmaceutically-acceptable salt thereof, or a compound of the formula (IV) as defined in claim 1, in preparation of a pharmaceutical composition for treating antihyperlipidemia and antiarteriosclerosis in mammals, preferably man.

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(71) Applicant: **FUJI PHOTO FILM CO., LTD.**
No. 210, Nakanuma
Minami-Ashigara-shi
Kanagawa-ken(JP)

(72) Inventor: **Alkawa, Kazuhiro, c/o Fuji Photo
Film Co., Ltd.**
No. 210, Nakanuma
Minami-Ashigara-shi, Kanagawa-ken(JP)
Inventor: **Aoki, Kozo, c/o Fuji Photo Film Co.,
Ltd.**
No. 210, Nakanuma
Minami-Ashigara-shi, Kanagawa-ken(JP)

(73) Representative: **Hansen, Bernd, Dr.**
Dipl.-Chem. et al
Hoffmann, Eitle & Partner,
Patentanwälte,
Arabellastrasse 4
D-81925 München (DE)

(54) **Pharmaceutical composition and method for treating hyperlipidemia and arteriosclerosis.**

(57) Disclosed are an antihyperlipidemia or antiarteriosclerosis agent comprising a certain benzimidazole or 2,2'-methylenediphenol derivative such as 5-dodecanoylamino-2-mercaptobenzimidazole or 2,2'-isobutylidenebis(4,6-dimethylphenol).

EP 0 583 665 A3



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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claims:
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions.
name(s):

see sheet -B-

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid.
namely claims:
- ☒ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.
namely claims: mentioned in item 1.



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LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

Annex Supplemental sheet B: EP 93112181.8

- 1.) Pharmaceutical compositions comprising a compound of the formulas I-III
(see claims 1 in part, 2-5, 9 in part, 10 in part)
- 2.) Pharmaceutical compositions comprising a compound of the formula IV (see claims 1 in part, 6-8, 9 in part, 10 in part)